

# C-reactive protein and cardiac repolarization in cirrhosis

Niya Emilova<sup>1</sup>, Dobrinka Dineva<sup>2</sup>, Maria Moneva-Sakelarieva<sup>3</sup>, Yozlem Kobakova<sup>3</sup>, Mariya Chaneva<sup>3</sup>, Ionko Ionchev<sup>3</sup>, Diana Slaveva<sup>3</sup>, Mihaela Popova<sup>3</sup>, Radoslav Tododrov<sup>3</sup>, Konstantin Kostov<sup>4</sup>, Silvia Sarakostova<sup>5</sup>

<sup>1</sup> University Emergency Medicine Hospital "Pirogov", Sofia, Bulgaria

<sup>2</sup> Department of Clinical Laboratory, University Emergency Medicine Hospital "Pirogov", Sofia, Bulgaria

<sup>3</sup> Clinic of Internal Medicine, University Emergency Medicine Hospital "Pirogov", Sofia, Bulgaria

<sup>4</sup> Department of General, Visceral and Emergency Surgery, University Emergency Medicine Hospital "Pirogov", Sofia, Bulgaria

<sup>5</sup> Clinic of Toxicology, University Emergency Medicine Hospital "Pirogov", Sofia, Bulgaria

**Corresponding author:** Niya Emilova, University Emergency Medicine Hospital "Pirogov", Sofia, Bulgaria; E-mail: [niaemilova@yahoo.com](mailto:niaemilova@yahoo.com)

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## Abstract

**Introduction:** The systolic and diastolic function of the left ventricle and the activation of the autonomic nervous system are main determinants of ventricular repolarisation. **Purpose:** We conducted an analysis of the association of inflammatory markers with indices of ventricular repolarisation (heart rate, duration of repolarisation period - QTc, dispersion of repolarisation - QTcd) as well as with prognostic scores in patients with alcoholic cirrhosis. A group of patients with chronic coronary disease (CAD) and another group with acute myocardial infarction (AMI) were used for comparison. **Results:** Procalcitonin correlated positively as tendency with Child-Pugh score in the patient group with alcoholic cirrhosis on therapy. Only WBC showed a trend for association with non-homogenous repolarization in the group of male patients with cirrhosis on therapy. Higher white blood count (WBC) was marginally related to shorter minimal repolarisation periods and with dispersion of repolarisation in AMI. Higher CRP was related as tendency with shorter minimal repolarisation periods, longer maximal repolarisation periods and correlated significantly positively with higher dispersion of repolarisation in AMI. Higher levels of CRP also correlated with prolonged maximal repolarization in stable CAD. **Conclusions:** The count of white blood cells and procalcitonin are associated with risk of complications in alcoholic cirrhosis. In patients with cirrhosis and infection on therapy, WBC is specific marker of increased dispersion of repolarisation. In contrast to cirrhosis, CRP is associated with the risk of ventricular arrhythmias in stable coronary disease, while both CRP and WBC correlated with repolarisation indices in acute myocardial infarction.

## Keywords

White blood cell count, C-reactive protein, procalcitonin, QTc, QTcd, cirrhosis, coronary disease, acute myocardial infarction

## Introduction

QTc is used as a measure of the duration of the period of ventricular repolarization adjusted to extremes in heart rate. The difference between the minimal and maximal QTc termed corrected QT dispersion (QTcd) reflects the disper-

sion of ventricular repolarization. Increased dispersion of repolarization is considered as prognostic index of the risk of sustained ventricular tachycardia and sudden cardiac death [1-3]. The systolic and diastolic function of the left ventricle and the activation of the autonomic nervous system are main determinants of ventricular repolarisation [1-3].

Observational studies in populations of patients with coronary disease suggested associations between repolarisation indices with acute myocardial ischemia, acute myocardial infarction and also with markers of myocardial injury [4-6]. QTcd is significantly higher in patients with myocardial infarction and heart failure with previous arrhythmic event [7].

Alcohol intoxication induces acute myocardial contractile abnormalities [8]. Chronic excessive alcohol consumption causes persistent inflammation in liver induced by toxic effect of alcohol on hepatocytes [9]. Liver cirrhosis is frequently complicated by bacterial infections [10]. Systemic inflammatory response was considered as underlying pathophysiological mechanism of left ventricular dysfunction in cases with alcoholic liver disease [9]. The duration of cardiac repolarisation (QTc) is usually abnormally long in cirrhosis of higher Child-Pugh and higher MELD scores. QTc increases with gastrointestinal bleeding, possibly due to related cardiac ischemia [2, 4, 11, 12]. In particular, systemic inflammation can significantly prolong QTc during acute infections, via cytokine-mediated changes in potassium channel expression [13]. Similar association, between prolonged QTc with increased inflammatory markers was reported in clinically active autoimmune diseases such as inflammatory bowel disease and rheumatoid arthritis [14, 15].

Beta-blockers reduce QTc dispersion in patients with chronic heart failure, with greater response in patients with ischemic cardiomyopathy [16]. Also, the addition of aldosterone inhibitor (spironolactone) and ACE inhibitor/AT receptor inhibitor significantly improves QT dispersion [17]. Beta-blockers and aldosterone inhibitors have same effects in cirrhosis.

There is limited data regarding arrhythmia risk prediction in cirrhosis and association of inflammation with the risk of ventricular arrhythmia. Our aim was to contrast inflammatory-repolarization relationships across diseases of different system localisation.

## Purpose

We conducted a retrospective cohort study of the association of inflammatory markers with indices of ventricular repolarisation (heart rate, duration of repolarisation period adjusted to heart rate - QTc, dispersion of repolarisation - QTcd) as well as with prognostic scores in patients with alcoholic cirrhosis. A group of patients with chronic ischemic heart disease and another group with acute myocardial infarction were used for comparison.

## Material and methods

A group of 19 male patients with alcoholic liver cirrhosis Child A, B and C class and 26 male patients with stable coronary disease (CAD) admitted to Clinic of Internal Medicine of Emergency Medicine Hospital 'Pirogov' for

infectious exacerbation of disease were analysed. A group of 60 male patients with acute myocardial infarction after primary percutaneous intervention with stent implantation without known infectious complications was used as comparison.

The diagnosis of liver cirrhosis was made based on the history of alcohol abuse, clinical and ultrasound signs of hepatomegaly, cirrhotic transformation of the liver, portal hypertension, ascites, peripheral oedema, jaundice. The alcoholic etiology of cirrhosis was supported by laboratory markers of persistent liver injury and indirect markers of alcohol consumption: increased mean volume of red blood cells (MCV), bilirubin, aspartate aminotransferase (ASAT),  $\gamma$ -glutamyl transferase (GGT), ratio of aspartate aminotransferase to alanine aminotransferase (ASAT/ALAT>1).

The scores used for the assessment of severity of cirrhosis included FIB-4 index, Child-Turcotte-Pugh (CTP) score and model of end-stage liver disease (MELD). They were calculated by means of an electronic calculator (MEDCalc). FIB-4 index is used for initial evaluation of liver fibrosis and combining data of age, ASAT, ALAT, platelet count of each patient with cirrhosis. Child-Turcotte-Pugh (CTP) score includes measures of plasma albumin, bilirubin, INR, data for diagnosed ascites, encephalopathy. This score is most widely used for liver cirrhosis staging but it does not consider renal function [18]. MELD uses the patient's values for serum bilirubin, serum creatinine, and the international normalized ratio for prothrombin time (INR) to predict survival [19].

The indices of repolarisation were measured from 12-lead conventional electrocardiography by one investigator. They were adjusted for extremes in heart rate by the use of Bazett's formula and of an e-calculator (MEDCalc). The duration of repolarisation period was defined by the interval between the beginning of Q-wave to the end of T-wave. The mean value of QT interval measured in all 12 leads was used in this analysis. The difference between the minimal and maximal QTc termed corrected QT dispersion (QTcd) was used as marker of the dispersion of ventricular repolarization.

The chemiluminescent microparticle immunoassay (CMIA) technology is used to quantitatively determine procalcitonin (PCT) in human serum and plasma. The principle of the method is described in details elsewhere [20].

The immunoturbidimetric method for measuring C-reactive protein (CRP) involves the formation of immunocomplexes between CRP in the test sample and specific antibodies. These complexes cause turbidity, which can be measured photometrically. The degree of turbidity is directly proportional to the CRP concentration in the sample [21].

Exclusion criteria for the study were: known or suspected neoplasm, operative treatment/trauma in the last month, active and severe chronic obstructive pulmonary disease, chronic renal failure with GFR <30 ml/min/m<sup>2</sup>, experienced stroke or other cerebral disease, which makes it difficult to assess the presence and degree of hepatic encephalopathy, long-standing diabetes mellitus with

suspicion of pronounced proteinuria, conditions of hypoaldosteronism, hypothyroidism, diseases that are associated with chronic inflammation, immune dysregulation and the need for immunosuppressive therapy (systemic connective tissue disease, known immune deficiencies, chronic glomerulonephritis, ulcerative colitis, etc.). Hypoaldosteronism was ruled out by lab tests; hypothyroidism was ruled out by lacking clinical history and signs of disease, also by normal thyroid tests in nearly one third of cirrhosis patients.

The statistical analysis included parametric ( $\chi^2$ - test, Fischer exact tests), non-parametric analyses (t - test - for the variables with normal distribution; Mann-Whitney U test - for the variables without normal distribution) of The correlation analysis included Perasion rho rank correlation was used when the variables were with normal distribution Spearman correlation, a nonparametric measure of the strength and direction of association was applied when there was at least one variable without normal distribution.

## Results

Patients with cirrhosis show more frequent anemia, lower hemoglobin, higher heart rates and higher levels of CRP (while WBC were similar in cirrhosis and CAD). The patients with stable CAD in our study showed worse renal function (Table 1). The minimal and maximal repolarisation periods were much longer in cirrhosis compared to stable CAD patients (Table 1).

Patients with cirrhosis were with lower hemoglobin, higher heart rates, much longer minimal and maximal repolarisation periods, higher dispersion of repolarisation compared to the patients with acute myocardial infarction, AMI (Table 2).

## Markers inflammation, indices of repolarisation and prognosis in alcohol liver disease and stable CAD

Higher WBC were marginally related with shorter minimal repolarisation periods in AMI. The higher WBC tend to correlated with non-homogenous repolarization in cirrhosis and were significantly associated with dispersion of repolarisation in AMI (Table 3, Figs 1, 2).

Higher CRP were related as tendency with shorter minimal repolarisation periods, longer maximal repolarisation periods and correlated significantly positively with higher dispersion of repolarisation in AMI (Fig. 2). The higher CRP also correlated with prolonged maximal repolarization in stable CAD (Table 4). CRP was not associated with repolarisation in the subset of patients with cirrhosis, according to this analysis (Table 4, Fig. 1).

**Table 1.** Characteristics of patients with cirrhosis and CAD, comparison.

Disease/variable	Cirrhosis n=19	CAD n=19	p
Age, years	58.3±14.4	63±13.1	0.326
Hypertension	12 (66.7%)	18 (90%)	0.117
Diabetes mellitus	7 (38.9%)	4 (20%)	NS
Anemia	16 (88.9%)	7 (35.6%)	0.001
Chronic kidney disease	5 (26.3%)	18 (72%)	NS
Creatinine	94.6±35.3	150.9±151.3	0.199
GFR, ml/min/m <sup>2</sup>	81.2±25.9	62.1±23.9	0.030
Hemoglobin	102.5±31	133.8±20.8	<0.0001
Procalcitonin	0.86 (0.18 - 4.41)		
WBC	6.9±1.7	8.3±2.2	0.292
CRP	1.74 (0.14-5.3)	0.34 (0.06-3.7)	0.035
Heart rate	77.6±13.6	71±9.9	0.077
QTcmin	445.4±58.7	401.7±44.9	0.011
QTcmax	548±42.9	505.8±42.9	0.003
QTcd	123.6±35.7	100.1±33.9	0.188
LV ejection fraction	47±7.7	52.2±11.3	0.292
β-blocker	9 (47.4%)	11 (52.4%)	1.000
Aldosterone antagonist	11 (57.9%)	0 %	NS
FIB4index	2.2 (1 - 13.4)		
ChildPugh	6.7±1.3		
MELD	14.7±5.5		

**Table 2.** Characteristics of patients with cirrhosis and acute myocardial infarction, comparison.

Disease/variable	Cirrhosis n=19	CAD n=19	p
Age, years	58.3±14.4	61±13.3	0.223
Hypertension	12 (66.7%)	19 (100%)	NS
Diabetes mellitus	7 (38.9%)	6 (28.6%)	NS
Anemia	16 (88.9%)	2 (11.1%)	NS
Creatinine	94.6±35.3	109.0±87	0.252
GFR, ml/min/m <sup>2</sup>	81.2±25.9	79.1±27.7	0.233
Hemoglobin	97 (62-151)	143 (122-197)	<0.0001
WBC	7.4 (3.9-8.9)	9 (6.1-13.4)	0.127
CRP	1.3 (0.14-7.0)	1.9 (0.7-16.7)	0.121
Heart rate	77.6±13.6	70.8±13.9	0.111
QTcmin	445.4±58.7	380.9±37.1	<0.0001
QTcmax	548±42.9	468.5±43.1	<0.0001
QTcd	123.6±35.7	89.9±26.6	0.029
LV ejection fraction	47±7.7	51.4±10.4	0.634
β-blocker	10 (27%)	5 (26.3%)	NS
Aldosterone antagonist	11 (57.9%)	0 %	NS

Higher PCT correlated significantly with higher heart rates and tended to correlate with greater severity of cirrhosis (Table 5).

Age was related with left ventricular (LV) systolic function (LV ejection fraction, LV EF). This correlation was inverse. It was a tendency and was observed only among the patients with coronary disease (p=- 0.476, p=0.062). Neither duration of repolarisation, dispersion of repolarisation nor any other variable showed significant correlation with age in the small groups with cirrhosis and coronary disease compared in our study.

**Table 3.** WBC, repolarization indices and other prognostic markers, correlation analysis.

Disease/variable	Cirrhosis		CAD		AMI	
	r	p	r	p	r	p
WBC						
Age	0.153	0.272	-0.187	0.442	-0.215	0.194
CRP	-0.120	0.318	-0.010	0.971	0.150	0.723
Heart rate	-0.076	0.389	0.014	0.951	0.084	0.370
QTcmin	-0.220	0.206	-0.076	0.771	-0.370	0.056
QTcmax	0.152	0.287	0.064	0.806	0.179	0.239
QTcd	0.352	0.091	0.116	0.657	0.562	0.008
LV ejection fraction	-0.300	0.129	0.351	0.200	-0.211	0.200
FIB4index	-0.223	0.187				
ChildPugh	-0.263	0.146				
MELD	-0.207	0.205				

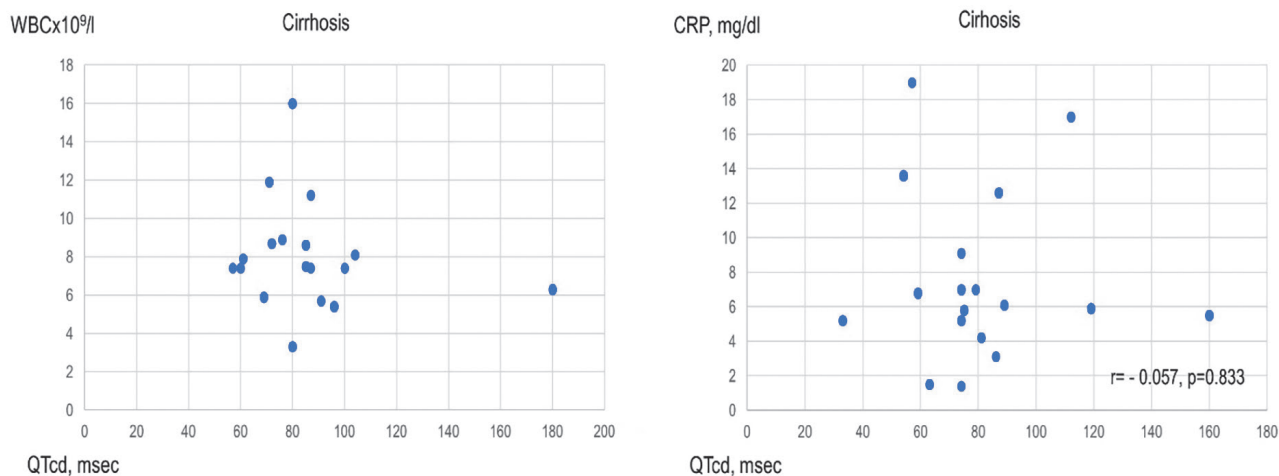
**Table 4.** CRP, repolarization indices and other prognostic markers, correlation analysis.

Disease/variable	Cirrhosis		CAD		AMI	
	r	p	r	p	r	p
CRP						
Age	0.065	0.797	0.046	0.860	0.245	0.156
Heart rate	0.154	0.568	0.314	0.237	0.270	0.130
QTcmin	-0.243	0.364	0.510	0.044	-0.371	0.059
QTcmax	-0.180	0.494	0.523	0.037	0.317	0.093
QTcd	-0.057	0.833	0.019	0.916	0.711	<0.0001
LV ejection fraction	0.285	0.215	0.350	0.241	-0.471	0.024
FIB4index	-0.200	0.426				
ChildPugh	0.198	0.432				
MELD	0.235	0.348				

## Discussion

The presented cohorts with cirrhosis and stable CAD differed by higher incidence of acute infectious disease at admission. The levels of CRP remained higher in the cirrhosis group after 7–10 days of antimicrobial treatment. Anemia was more commonly diagnosed in the group with cirrhosis in contrast to CAD. The therapy with  $\beta$ -blocker was underused in the settings of cirrhosis. Consistently, the heart

rates of our patients with cirrhosis tended to be substantially higher compared to the patients with CAD. Most often, the patients with cirrhosis and clinically significant portal hypertension have more advanced hyperdynamic circulation than do those without severe portal hypertension [1,22]. Thus, a much greater hepatic venous pressure gradient reduction by  $\beta$ -blockers is expected in patients with clinically significant portal hypertension than in those without [22]. The main determinants of the corrected QT interval and the corrected dispersion of repolarization are the systolic and diastolic function of left ventricle and the activation of the autonomic nervous system [1-3]. The reduction of QTcd by  $\beta$ -blockers suggests a prophylactic effect of  $\beta$ -blockers regarding severe arrhythmias due to inhomogeneous ventricular repolarization. Beta-blockers shorten QTc in cirrhosis similar to CAD [11]. We can speculate that unopposed sympathetic system overactivity augmented during acute infection could be confounding factor which contributed to an association of certain inflammatory markers (white blood cells) with dispersion of repolarisation and arrhythmia risk in the group with cirrhosis to in contrast to CAD. Higher heart rates lead to shorter minimal repolarisation periods and thus to increased QTcd. In addition, repolarisation period increases in cirrhosis complicated with gastrointestinal bleeding or infection possibly due to overt cardiac ischemia [23]. The prevalence myocardial injury in patients with infectious disease was found to be up to 36% [24]. According to previous studies, markers of cardiac dysfunction (hs-TnT) and inflammation (CRP) were significantly associated with severity in liver disease, degree of portal hypertension and survival in cirrhosis [23]. Provided that there was high rate of infectious complications in the investigated cohorts, we tested for significance the association of markers of inflammation with left ventricular systolic function in cirrhosis. Troponin was assessed in few patients with cirrhosis in the cohort with cirrhosis analysed and we found out that troponin values varied within reference limits. Any substantial correlation of CRP and WBC with left ventricular ejection function was not found.



**Figure 1.** QTcd and markers of inflammation in patients with cirrhosis on therapy.

Despite that, WBC at the time of cirrhosis decompensation emerged as predictor of non-homogenous repolarisation, and thus of arrhythmia risk.

We observed a positive correlation of the dispersion of repolarisation with WBC in the group of patients with cirrhosis and a lack of correlation with CRP in the same cohort. This correlation could be marker of ongoing remote myocardial ischemia secondary to chronic anaemia and hyperkinetic circulation in patients with cirrhosis and acute infection rather than to co-morbid coronary artery disease. There are two reasons supporting such hypothesis. First, the existing literature link higher CRP with prolongation of QTc interval exclusively in patients with coronary artery disease only in the settings of systemic inflammatory conditions such as sepsis and COVID-19 infection [25, 26]. Secondly, the site of production and the site of metabolism of CRP are still not well defined [27]. Currently, it is thought that CRP is produced exclusively by hepatocytes and human macrophages. Nevertheless, studies suggest a variety of other sites of production of CRP by locally distributed macrophages including coronary-arteries, inflamed kidneys, adipose tissue [27]. In coronary disease, macrophages accumulate with expansion of the lipid core of atherosclerotic plaques [28] and increase further at the time of acute coronary plaque rupture and thrombosis. The significant elevation of CRP levels reported after 48 hours of plaque rupture in acute myocardial infarction (AMI) [29] was proved to be due to response of immune system to myocardial necrosis. Myocardial ischemia leads to higher QT dispersion. The latter aids in diagnosing acute coronary syndrome in patients presenting with chest pain [5]. Also, there is inverse correlation between the size of myocardial infarction (assessed by the elevation in cardiac enzymes) with QT dispersion in patients with non-ST elevation myocardial infarction [6]. We also obtained strong CRP-QTcd correlation ( $r=0.711$ ,  $p<0.0001$ ). Possible confounder of this association is the developed phase of inflammatory response to the infarct zone. CRP and WBC were measured immediately after percutaneous intervention. In the patient

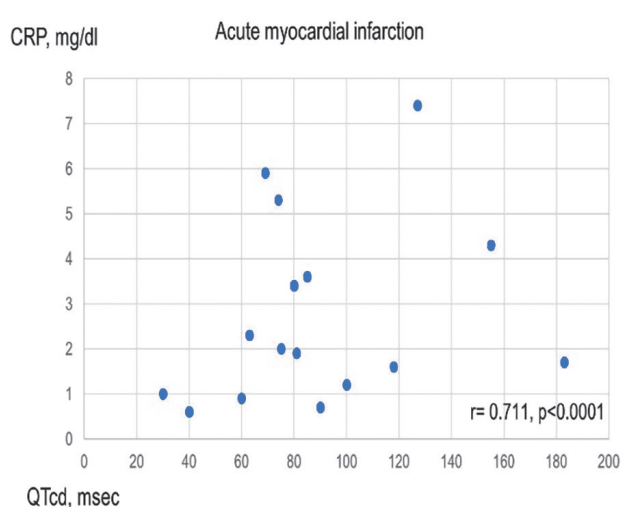
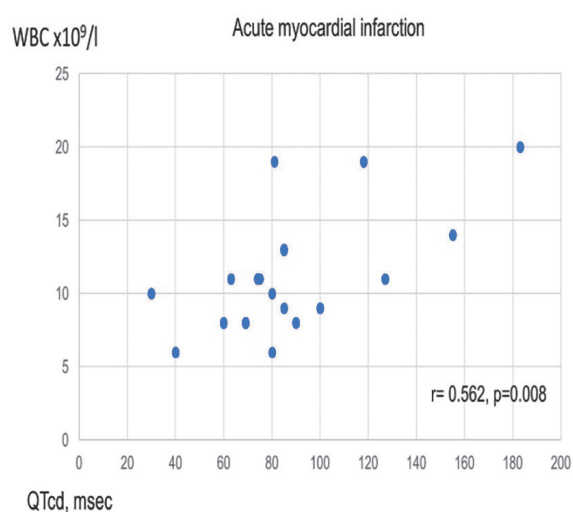
**Table 5.** Procalcitonin correlation with repolarization indices and other prognostic markers in patients with cirrhosis.

Disease	Cirrhosis	
	r	p
Heart rate	0.507	0.022
QTcmin	-0.094	0.365
QTcmax	0.158	0.280
QTcd	0.199	0.230
LV ejection fraction	0.268	0.158
FIB4index	0.137	0.294
ChildPugh	0.330	0.077
MELD	-0.001	0.499

group with cirrhosis the initial treatment with antibiotics before obtaining blood samples for CRP and PCT blurred the relationship of CRP with repolarisation indices. Other cause of significant correlation is the same location (the heart) of inflammatory response and the functional abnormality (increased dispersion of repolarisation) in the acute phase of myocardial infarction.

We also confirm the significance of acute inflammation (WBC, CRP, procalcitonin) as factor for future complications in cirrhosis. The levels of circulating inflammatory molecules such as C-reactive protein and procalcitonin were elevated in patients with alcohol liver disease and cirrhosis. Assessment of plasma levels of CRP and PCT directly correlated with prognosis in cirrhosis [30, 31].

The correlation of procalcitonin with heart rate ( $r=0.507$ ,  $p=0.022$ ) is interesting and novel finding in this study. Discrepancies between plasma PCT and CRP levels are common in acute illness. PCT is elevated in bacterial infections and sepsis and may help in discriminating between bacterial infection and immune system activation (e.g. in an autoimmune disease). Higher heart rates are characteristic feature of bacterial infection in which PCT is elevated. However, the relationship PCT and heart rate could be more complex and possibly includes sympathetic autonomic nervous system activation.



**Figure 2.** QTcd and markers of inflammation in patients in acute myocardial infarction.

## Conclusions

The count of white blood cells and procalcitonin is associated with the severity in alcoholic liver disease and the risk of complications. In patients with cirrhosis and infection, WBC is specific marker of increased dispersion of repolarisation. In contrast to cirrhosis, CRP is associated with the risk of ventricular arrhythmias in stable coronary disease, while both CRP and WBC correlated with repolarisation indices in acute myocardial infarction. Treatment with  $\beta$ -blockers could reduce the risk of arrhythmia in patients with cirrhosis.

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## Additional information

### Conflict of interest

The authors have declared that no competing interests exist.

### Ethical statements

Clinical trials: Approval by the Committee of Ethics of University Emergency Medicine Hospital 'Pirogov' as part of a research project 'Gonadal steroids as epiphenomenon of inflammation in patients with alcoholic liver disease' (incoming № EK-12-24/07-11-2024).

The authors declared that no experiments on humans or human tissues were performed for the present study.

Informed consent from the humans, donors or donors' representatives: The signed informed consents are kept by the leading researcher. Blind copies of all informed consents can be made available upon request to the journal.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

### Use of AI

No use of AI was reported.

## Funding

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## Author contributions

Conceptualization: NE. Data curation: DS, MC, RT, II, DD, NE, SS, KK, YK, MP. Formal analysis: YK, MC, DS, DD, NE, KK, RT, II, MMS, SS, MP. Funding acquisition: NE. Investigation: MMS, KK, NE, YK, MC, MP, SS, II, RT, DD, DS. Methodology: DD, KK, NE, SS. Project administration: DS, MC. Resources: MMS, RT, MC, KK, SS. Software: RT, NE. Supervision: MP, DD, II. Validation: DS, DD, YK, MC, MP, NE, MMS, RT, KK. Visualization: SS, DS. Writing - original draft: NE. Writing - review and editing: MP, SS, KK, II, MMS, RT, DD, MC, DS, YK.

## Author ORCIDiDs

Niya Emilova  <https://orcid.org/0000-0003-1878-9807>

Dobrinka Dineva  <https://orcid.org/0009-0005-1019-128X>

## Data availability

All of the data that support the findings of this study are available in the main text or Supplementary Information.

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